Sedative / Hypnotic

Therapeutic Class Review (TCR)

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FDA-APPROVED INDICATIONS

Drug	Manufacturer	Adjunct to anesthesia and perioperative sedation	Short-term treatment of insomnia	Treatment of insomnia	Treatment of Non-24-Hour Sleep-Wake Disorder
doxepin (Silenor®)[1]	Somaxon			X	
estazolam[2]	generic		X		
eszopiclone (Lunesta™)[3]	generic			X	
flurazepam (Dalmane®)[4]	generic		X		
quazepam (Doral®)[5]	generic		X		
ramelteon (Rozerem™)[6]	Takeda			X	
tasimelteon (Hetlioz™)[7]	Vanda				X
temazepam (Restoril®)[8]	generic		X		
triazolam (Halcion®)[9]	generic		X		
zaleplon (Sonata®)[10]	generic		X		
zolpidem (Ambien®)[11]	generic		X		
zolpidem sublingual (Edluar®)[12]	Meda		X		
zolpidem sublingual (Intermezzo®)[13]	Purdue			X Middle of the night awakening	
zolpidem (Zolpimist™)[14]	ECR		X		
zolpidem ER (Ambien® CR)[15]	generic			X	

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OVERVIEW

Insomnia is a symptom complex that comprises difficulties falling asleep, staying asleep, or non-refreshing sleep in combination with daytime dysfunction or distress. The symptom complex can be an independent disorder (primary insomnia) or the result of another condition (secondary insomnia).[16] Insomnia is commonly divided into three types based on duration. Transient insomnia lasts up to one week and is often referred to as adjustment sleep disorder because it is caused most often by an acute situational stress, such as a test or deadline. It is often recurrent with the same or similar stresses. The second type, short-term insomnia, by definition lasts one to six months and is usually associated with more persistent stressful situational (death or illness) or environmental (noise) factors. Finally, chronic insomnia is insomnia lasting more than six months.

Treatment for insomnia should first consist of identification and treatment/control of secondary sources. Whenever possible, use of non-pharmacological measures should be used to treat insomnia. Stimulus control, progressive muscle relaxation, sleep restriction, cognitive behavioral therapy (CBT), multicomponent therapy (without CBT), paradoxical intention, and biofeedback have been shown to be beneficial and are all recommended by the American Academy of Sleep Medicine (AASM).[17] When such measures fail to address the condition, use of pharmacologic hypnotics may be necessary.

The 2006 AASM guidelines recommend a number of behavioral strategies and pharmacological agents for the treatment of insomnia. Further clinical guidance identifies psychological and behavioral strategies are effective in both primary and secondary insomnia as are pharmacological interventions. Initial behavioral interventions should include stimulus control therapy or relaxation therapy or a combination of therapies referred to as cognitive behavioral therapy for insomnia (CBT-I). Cognitive behavioral therapy for insomnia includes traditional CBT, stimulus control, and sleep restriction therapy (with or without relaxation therapy). If these strategies are not effective other behavioral therapies not previously attempted or combined treatment may be applied. Additionally recommendations are provided for pharmacological treatment, which include short-term hypnotic therapy or ramelteon.[18] The Agency of Healthcare Research and Quality (AHRQ), published a comparative effectiveness review for the off-label use of atypical antipsychotics and noted evidence for such practice is very low, and may be inefficacious for treatment of insomnia.[19]

The American Academy of Sleep Medicine 2008 treatment guidelines for chronic insomnia do not distinguish amongst the pharmacological agents in this review.[20] There are considerations to be made for individual patients, but there is no clear agent for the population at large.

Non-24-hour sleep-wake disorder (non-24) is a chronic circadian rhythm disorder that causes problems with the timing of sleep and sleep patterns of people who are totally blind.21 The National Organization for Rare Disorders (NORD) states that the condition is characterized by the failure of a person's biological clock to synchronize to a 24-hour day light-dark cycle because light does not enter their eyes.

Those with the disorder may have difficulty falling or staying asleep, and may wake up feeling as if they need more rest. People with non-24 may find their sleep patterns reversed (e.g., needing to sleep during the day and to be awake at night). Non-24 can occur at any age and affects about 100,000 individuals in the United States

This review will focus on those agents indicated for sleep disorders and contemporary treatment in adults.

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PHARMACOLOGY

Benzodiazepines are believed to potentiate gamma aminobutyric acid (GABA) neuronal inhibition. The sedative and anticonvulsant actions of these drugs involve GABA receptors located in the limbic, neocortical, and mesencephalic reticular systems. At least two benzodiazepine receptor subtypes have been identified in the brain, BZ-1 and BZ-2. BZ-1 is thought to be associated with sleep mechanisms while BZ-2 is thought to be associated with memory, motor, sensory, and cognitive functions. Benzodiazepines generally decrease the time to onset of persistent sleep (sleep onset latency, SOL) and reduce the number of awakenings.[22]

Although structurally different from the benzodiazepines and from one another, the cyclopyrrolone hypnotics (Z-drugs), eszopiclone (Lunesta), zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Zolpimist, and Intermezzo), are all active at the GABA-BZ receptor complex.[23] Unlike the benzodiazepines, these newer agents bind selectively to the BZ-1 receptor.

Ramelteon (Rozerem) is a highly selective and potent agonist of the MT1 and MT2 melatonin receptors, which are believed to be involved in the regulation of the circadian rhythm.[24] Tasimelteon (Hetlioz) is also an agonist at the MT1 and MT2 receptors, with greater affinity for the MT2 receptor.[25] The MT1 receptor is believed to regulate sleepiness, whereas the MT2 receptor is thought to help the body shift between day and night. Ramelteon has been reported to have greater affinity, selectivity, and potency than melatonin for the MT1 receptor, resulting in a better ability to induce sleep onset. Ramelteon has shown no affinity for the GABA-receptor complex, which is the primary target area for most of the other agents in this class.[26]

Doxepin (Silenor) is a new formulation of the sedative tricyclic antidepressant, and is now approved for treatment of insomnia, in particular those with sleep maintenance problems. Doxepin binds with a high affinity to H_1 histamine receptors where it functions as an antagonist. While the exact mechanism of action as a sedative is unclear, it is thought the antagonistic activity at the H_1 receptor results in its sedative effect.[27]

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Pharmacokinetics

Drug	Onset of Action (minutes)	Duration of Action (hours)	Half-Life of Parent Compound (hours)	Active Metabolite(s) (Half-Life)	Metabolism
doxepin (Silenor)[28]	n/a	3 (delayed in presence of high fat meal)	15.3	N-desmethyldoxepin	oxidation and demethylation
estazolam[29,30]	15-120	6-8	14.4-15	None	CYP 3A4
eszopiclone (Lunesta)[31,32]	≤30	6-8	6	(S)-zopiclone-N-oxide (S)-N-desmethylzopiclone	CYP 3A4 CYP 2E1
flurazepam[33]	30-60	7-10	2.3	N_1-desalkylflurazepam (47-100 hrs; up to 160 hrs in elderly) N_1-hydroxyethylflurazepam (2-4 hrs)	oxidation
quazepam (Doral)[34]	20-60	7-10	39	2-oxoquazepam (39 hrs) N-desalkyl-2-oxoquazepam (73 hrs)	hepatic
ramelteon (Rozerem)[35]	≤30	nr	1-2.6	MII (2-5 hrs)	oxidation CYP 1A2
tasimelteon (Hetlioz)[36]	n/a	nr	1.3+0.4	None	oxidation and oxidative dealkylation
temazepam[37]	15-120	6-8	3.5-18.4	None	conjugation
triazolam[38]	15-30	1.7-3	1.5-5.5	None	oxidation CYP 3A4
zaleplon (Sonata)[39,40]	10-30	4	1	None	aldehyde oxidase CYP 3A4
zolpidem (Ambien)[41] zolpidem ER (Ambien CR)[42]	<30-96 (delayed in presence of food)	8	2.5-2.6 2.8	None	CYP 3A4
zolpidem sublingual (Edluar)[43]	delayed the in presence of food	8	2.65-2.85	None	CYP 3A4
zolpidem sublingual (Intermezzo)[44,45]	37 delayed the in presence of food	4	2.5	None	CYP 3A4

Zolpidem (Zolpimist) is bioequivalent to zolpidem (Ambien) tablets.[46]

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Hetlioz (tasimelteon) involves the control of circadian rhythms. Because of individual differences in circadian rhythms, drug effect may not occur for weeks or months.[47]

Zolpidem ER (Ambien CR) is a coated two-layer tablet with one layer that releases the drug content immediately and another layer that slowly releases additional drug beyond three hours after administration.[48] Compared to the immediate release formulation, the peak concentration of zolpidem ER is reached at a later time (2.4 versus two hours; p<0.004) and is approximately 13 percent lower.[49]

The difference in zolpidem (Ambien, Ambien CR, Edluar, Zolpimist, and Intermezzo) dosing between men and women is due to the lower rate of clearance by women compared to men.[50]

CONTRAINDICATIONS/WARNINGS[51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64]

These drugs, with the exception of zolpidem SL (Intermezzo), should all be administered immediately before going to bed or after the patient has gone to bed and experienced difficulty falling asleep. Zolpidem SL (Intermezzo) should be utilized for middle of the night awakenings when the patient has more than four hours before planned waking time. All these agents may result in short-term memory impairment, hallucinations, impaired coordination, dizziness, and light-headedness. The FDA-approved hypnotics (including non-benzodiazepine sedative hypnotics, hypnotics, and doxepin) includes a warning regarding complex sleep-related behaviors such as sleep-driving, making phone calls, sexual activity, and preparing and eating food while asleep and often patients have no memory of these events. These behaviors are more likely to occur when the sedative-hypnotic is taken concurrently with alcohol or other CNS depressants. Patients often have no memory of these events. The drugs in this class should all be used at the lowest effective dose and only after careful assessment of sleep disturbances for cause, emergence, or worsening of psychiatric or physical disorders, behavioral changes, amnesia, and withdrawal symptoms. Patients whose insomnia fails to remit after seven to 10 days of treatment with a sedative-hypnotic may have a primary psychiatric or medical illness that should be evaluated.

All of the agents in this class except doxepin (Silenor) and tasimelteon (Hetlioz) have a warning about their potential for anaphylaxis and angioedema, which can occur as early as the first dose.

Benzodiazepines are contraindicated in patients with suspected or established sleep apnea. Ramelteon, doxepin, or tasimelteon have not been studied in subjects with severe sleep apnea or severe COPD and they are not recommended for use in those populations.

Ramelteon (Rozerem) is not a controlled substance. No difference in subjective responses indicative of abuse potential was found between ramelteon and placebo at doses up to 20 times the recommended therapeutic dose.[65]

Ramelteon and zaleplon (Sonata) should not be used in patients with severe hepatic impairment. Patients with untreated narrow angle glaucoma or severe urinary retention should not use doxepin (Silenor).

All sedative/hypnotics should be administered with caution to patients exhibiting signs and symptoms of depression. Suicidal tendencies may be present in such patients, and protective measures may be required. Intentional overdose is more common in this group of patients; therefore, the smallest amount of drug that is feasible should be prescribed for the patient at any one time. Special attention should be given to doxepin (Silenor), because the active ingredient is a tricyclic antidepressant.

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Administration of antidepressants in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders could also increase suicidal thoughts and actions.

In January 2013, the FDA announced lower dosing recommendations for zolpidem due to new data showing that blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving.[66] Women appear to be more susceptible to this risk as they eliminate zolpidem more slowly compared to men. The recommended dose of zolpidem for women should be lowered from 10 mg to 5 mg for immediate-release products (Ambien, Edluar, and Zolpimist) and from 12.5 mg to 6.25 mg for extended-release products (Ambien CR). For men, health care professionals should consider lower zolpidem doses, but it is not required. The recommended doses of Intermezzo did not change. At the time of Intermezzo's approval, the label already recommended a lower dosage for women than for men. For zolpidem and other insomnia drugs, the lowest dose should be prescribed that treats the patients' symptoms.

Patients with compromised respiratory function should be cautioned prior to the use of zolpidem (Ambien, Ambien CR, Edluar, Zolpimist) since respiratory depression can occur.

Risk Evaluation and Mitigation Strategies (REMS)

Medication Guides are to be dispensed with doxepin, ramelteon, quazepam, flurazepam, eszopiclone, temazepam, triazolam, and zolpidem products.

DRUG INTERACTIONS[67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80]

Drugs in this class should be used with caution in patients receiving other CNS depressants as the effects may be additive, resulting in decreased alertness and impaired psychomotor performance.

Increased CNS depressant effects of the benzodiazepines that are metabolized by oxidation have been reported when coadministered with isoniazid, oral contraceptives, cimetidine, and disulfiram.

Estazolam, eszopiclone (Lunesta), ramelteon (Rozerem) and its active MII metabolite, tasimelteon (Hetlioz), triazolam, zaleplon (Sonata), and zolpidem (Ambien, Ambien CR, Edluar, Zolpimist, Intermezzo) are substrates for the CYP450 3A4 enzyme. As such, inducers of CYP450 3A4 (e.g., rifampin) increase the clearance and reduce the bioavailability of these agents by approximately 80 percent. Inhibitors of CYP450 3A4 (e.g., cimetidine, clarithromycin, ketoconazole) increase the bioavailability of these drugs by up to 84 percent.

Ramelteon and tasimelteon is contraindicated for concomitant use with fluvoxamine, a strong CYP1A2 inhibitor. It should be used with caution in patients taking less strong CYP1A2 inhibitors. Administration of ramelteon with fluconazole increases the bioavailability of ramelteon and the MII metabolite by approximately 150 percent. Concurrent administration of triazolam with efavirenz, delavirdine, azole antifungals, nefazodone, protease inhibitors, and any drugs that significantly impair the CYP3A mediated oxidative metabolism are contraindicated. Caution is recommended when administering triazolam with grapefruit juice, fluvoxamine, diltiazem, verapamil, amiodarone, nicardipine, nifedipine, cimetidine and ranitidine because these agents can increase plasma concentration of triazolam.

Doxepin (Silenor) is primarily metabolized by CYP2C19 and CYP2D6 hepatic cytochrome P450 isozymes. Inhibitors of these isozymes may increase the exposure of doxepin in patients. Concomitant administration of doxepin and alcohol, CNS depressants, and sedative antihistamines has shown increased sedative effects. Severe hypoglycemia has been reported with the simultaneous use of

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tolazamide. Using doxepin and cimetidine together has caused an increased exposure to doxepin. Patients should not use Monoamine Oxidase Inhibitor (MAOI) medications within 14 days of doxepin.

The efficacy of tasimelteon may be reduced in patients with concomitant beta adrenergic receptor antagonists.

Adverse Effects

Drug	Headache	Myalgia	Amnesia	Dizziness	Daytime Drowsiness/ Somnolence
doxepin (Silenor)[81]	nr	<2	nr	reported	6-9
estazolam[82]	16 (27)	≤1	≤1	7 (3)	3 (2)
eszopiclone (Lunesta)[83]	16-20 (13)	nr	nr	5-7 (4)	8-10 (3)
flurazepam[84]	reported	nr	reported	reported	reported
quazepam (Doral)[85]	4.5 (2.2)	nr	reported	1.5 (<1)	12 (3.3)
ramelteon (Rozerem)[86]	<1	nr	nr	4 (3)	3 (2)
tasimelteon (Hetlioz)[87]	17 (7)	nr	nr	nr	nr
temazepam[88]	8.5 (9.1)	nr	<0.5	4.5 (3.3)	2.5 (1.1)
triazolam[89]	9.7 (8.4)	nr	reported	7.8 (3.1)	nr
zaleplon (Sonata)[90]	30-42 (35)	7 (4)	2-4 (1)	7-9 (7)	nr
zolpidem (Ambien, Edluar, Zolpimist)[91, 92, 93]	7 (6)	>1	1 (0)	5 (1)	8 (6)
zolpidem (Intermezzo)[94]	3 (1)	nr	nr	nr	nr
zolpidem ER (Ambien CR)[95]	14-19 (11-16)	<1-4 (0)	1-3 (0)	8-12 (3-5)	6-15 (2-5)

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported.

For eszopiclone (Lunesta), 16 to 34 percent of patients reported a dose-related unpleasant taste as compared to three percent of placebo patients. Dose-related respiratory infection has been reported in five to ten percent of patients taking eszopiclone compared to three percent of patients taking placebo. Anxiety has been reported in one to 3.7 percent of patients receiving eszopiclone compared to zero percent of patients taking placebo in one six-week placebo controlled trial.

Nightmares have been reported with the use of tasimelteon (Hetlioz) and zaleplon (Sonata).

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SPECIAL POPULATIONS[96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106]

Pediatrics

The incidence of insomnia in children ranges from one to six percent; in children with neurodevelopmental or psychiatric comorbidities, the incidence is as high as 50 to 75 percent.[107, 108, 109] Insomnia in children may result in irritability, restlessness, lack of concentration, suicide risk, and poor memory.[110]

Eszopiclone (Lunesta) failed to demonstrate efficacy in controlled clinical studies of pediatric patients with Attention Deficit/Hyperactivity (ADHD) associated insomnia.

Additionally, flurazepam (Dalmane) is indicated for treatment of insomnia in children older than 14 years old.

The American Academy of Sleep Medicine's task force on Pharmacotherapy in Pediatric Sleep Medicine published guidelines in 2005 that do not recommend any one hypnotic over another for use in children.[111] Rather, the consensus statement urges caution when using any of these drugs for the pediatric patient and calls for additional research to be completed.

Guidelines from the 2006 National Sleep Foundation, state that there is a need for pharmacologic management of pediatric insomnia.[112] Acknowledging that there is an absence of pharmaceuticals indicated for hypnotic use in the pediatric population, this organization stated that there is a need for trials to confirm the safety and efficacy of such agents in these patients.

A survey of 671 primary care pediatricians found that more than 75 percent had prescribed nonprescription medications, and more than half had prescribed prescription medications for pediatric insomnia.[113] Most commonly, these agents were prescribed for acute pain and travel, followed by children with special needs. Antihistamines were the most common nonprescription medications for sleep, followed by melatonin and herbal remedies. Alpha-agonists were the most frequently prescribed prescription sleep medication.

Pregnancy

Zolpidem (Ambien, Edluar, Zolpimist, Intermezzo), zolpidem ER (Ambien CR), (doxepin (Silenor), eszopiclone (Lunesta), ramelteon (Rozerem), tasimelteon (Hetlioz) and zaleplon (Sonata) are Pregnancy Category C. While the other benzodiazepine hypnotics are Pregnancy Category X, flurazepam has not been assigned a pregnancy category but is contraindicated in pregnancy.

Hepatic Impairment

Patients with hepatic impairment may display higher doxepin (Silenor) concentrations than healthy patients. Patients with hepatic impairment should initiate treatment at the lowest recommended daily dosage and monitor for adverse daytime effects.

In patients with severe hepatic impairment, the bioavailability of eszopiclone is increased two-fold compared with healthy volunteers; time-to-peak and peak concentrations remain unchanged.

Ramelteon should be used with caution in patients with moderate hepatic impairment; exposure to ramelteon was increased nearly four times normal amounts when given to patients with mild hepatic impairment.

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The bioavailability of zaleplon is increased up to 400 percent in patients with compensated cirrhosis and 700 percent with decompensated cirrhosis.

In patients receiving zolpidem (Ambien, Edluar, Zolpimist) who have hepatic insufficiency, the daily dose should not exceed 5 mg, and for the controlled release tablet the maximum dose should not exceed 6.25 mg. For zolpidem sublingual (Intermezzo) in those with hepatic insufficiency the maximum once daily dose should not exceed 1.75 mg.

Dose adjustment is not necessary in patients with mild or moderate hepatic impairment. Tasimelteon (Hetlioz) has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, tasimelteon is not recommended for use in patients with severe hepatic impairment.

Japanese Patients

In Japanese adults, the maximum plasma concentration of zaleplon is increased by 37 percent. The effect of other ethnic groups has not been widely studied.[114]

Geriatrics[115, 116, 117]

Patients over the age of 65 years may demonstrate an increase in total exposure to sedative/hypnotic agents. Dosing for the benzodiazepines should commonly begin at the lowest effective dose for these patients. Ramelteon and doxepin may be an exception as they did not show any overall differences in safety and efficacy between elderly and younger adult patients.

Smokers[118]

Smoking causes induction of CYP1A2 levels. The exposure of tasimelteon (Hetlioz) in smokers was lower than in non-smokers and therefore the efficacy of tasimelteon may be reduced in smokers.

DOSAGES[119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134]

Drug	Bedtime Dose	Dose Adjustment	Availability
doxepin (Silenor)	6 mg Take 30 minutes before bedtime and not within three hours of a meal	Elderly: begin with 3 mg and increase to 6 mg if required 3 mg if clinically indicated for individual patients	Tablet: 3 mg, 6 mg
estazolam	1-2 mg	Elderly, underweight, or debilitated: 0.5-1 mg	Tablet: 1mg, 2 mg
eszopiclone* (Lunesta)	recommended starting dose: 1 mg	Dosing can be raised to 2 mg or 3 mg if clinically indicated Elderly: total dose should not exceed 2 mg Severe hepatic impairment: should not exceed 2 mg Concurrent use with strong CYP 3A4 inhibitor: should not exceed 2 mg	Tablet: 1 mg, 2 mg, 3 mg
flurazepam (Dalmane)	15-30 mg	Elderly and adolescents: 15 mg	Capsule: 15 mg, 30 mg

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Dosages (continued)

Drug	Bedtime Dose	Dose Adjustment	Availability
quazepam (Doral)	15 mg, dose may be reduced to 7.5 mg in some patients based on individual response	Elderly: 7.5 mg, dose may be increased to 15 mg if 7.5 mg is ineffective after one to two nights	Tablet: 15 mg
ramelteon (Rozerem)**	8 mg	--	Tablet: 8 mg
tasimelteon (Hetlioz)	20 mg	--	Capsule: 20 mg
temazepam (Restoril)	7.5-30 mg	Elderly and debilitated: start at 7.5 mg initially until individual responses are determined	Capsule: 7.5 mg, 15 mg, 22.5 mg, 30 mg
triazolam (Halcion)	0.125-0.5 mg	Elderly or debilitated: 0.125 - 0.25 mg	Tablet: 0.125 mg, 0.25 mg
zaleplon (Sonata)***	10-20 mg May also use 5 mg for low weight individuals	Elderly, low-weight or hepatic impairment: 5-10 mg Concurrent use of cimetidine: Initial dose: 5 mg Mild to moderate hepatic impairment: 5 mg	Capsule: 5 mg, 10 mg
zolpidem* (Ambien, Edluar, Zolpimist)	**Men:** 5 or 10 mg **Women:** 5 mg The 5 mg dose can be increased to 10 mg if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness	Elderly, debilitated, or hepatic insufficiency: 5 mg once daily immediately before bedtime Concurrent CNS depressants: dosage adjustment may be necessary	Tablet: 5mg, 10 mg Sublingual Tablet: 5 mg, 10 mg Oral Spray: 5 mg
zolpidem ER (Ambien CR*)	**Men:** 6.25 or 12.5 mg **Women:** 6.25 mg The 6.25 mg dose can be increased to 12.5 mg if needed, but the higher dose is more likely to impair next morning driving and other activities that require full alertness	Elderly, debilitated, or hepatic insufficiency: 6.25 mg once daily immediately before bedtime Concurrent CNS depressants: dosage adjustment may be necessary	Tablet: 6.25 mg, 12.5 mg
zolpidem sublingual (Intermezzo)	**Men:** 3.5 mg **Women:** 1.75 mg Take if there is more than 4 hours remaining before planned time of waking	Elderly, hepatic insufficiency, concurrent CNS depressants: 1.75 mg	Sublingual Tablets: 1.75 mg, 3.5 mg

* Should be taken on empty stomach to avoid delayed onset of action.

**Due to a 31 percent increase in bioavailability when given with a high-fat meal, ramelteon (Rozerem) should not be taken with or immediately after such a meal.

***Taking zaleplon (Sonata) or eszopiclone (Lunesta) with or immediately after a heavy, high fat meal results in slower absorption and would be expected to reduce its effect on sleep latency.

Since many of the adverse effects to the sedative/hypnotics appear to be dose-related, therapy should usually be initiated with a low dose and then maintained at the lowest effective dose, especially in the elderly. Continuous use should be avoided; patients should be encouraged to use these medications

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only when necessary. Use for more than three weeks should be avoided and monitored if a longer duration is necessary. These drugs should never be combined with alcohol consumption.

CLINICAL TRIALS

Search Strategies

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled comparative trials for FDA-approved indications are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance. Many of the trials with agents in this class were performed in an open-label manner; introduction of bias must be considered when evaluating study findings.

Comparisons of Benzodiazepines

estazolam and flurazepam

The hypnotic efficacy of estazolam 1 mg and 2 mg was compared to flurazepam 30 mg and placebo in a randomized, double-blind, seven night study that involved 223 patients with insomnia.[135] On subjective assessments of the patients, no differences were noted between estazolam 2 mg and flurazepam 30 mg on any of six sleep parameters. Patients who received estazolam 1 mg rated their sleep significantly better than did patients who were receiving placebo on all parameters except sleep onset latency (SOL). Global evaluation of the physicians indicated significant improvement in quality of sleep, sleep duration, and nocturnal awakenings in all three active treatment groups; estazolam 2 mg and flurazepam 30 mg decreased SOL significantly. Adverse events were reported by 54 percent of patients receiving estazolam 1 mg, 58 percent of those receiving estazolam 2 mg, and 68 percent of those receiving flurazepam 30 mg. The incidence of adverse events in the placebo group was 43 percent.

In a double-blind trial, 229 patients with insomnia were randomized to receive estazolam 2 mg, flurazepam 30 mg, or placebo for seven consecutive nights.[136] The analysis of efficacy was based on patients' daily assessments of sleep and investigators' global evaluations. The patient subjective questionnaire indicated that estazolam and flurazepam significantly improved all parameters ($p<0.05$) as compared to placebo. A marked or moderate improvement in sleep was reported by 81, 78 and 36 percent estazolam, flurazepam, and placebo recipients, respectively. There were no significant differences in hypnotic effect between estazolam and flurazepam. All efficacy parameters of the investigators' global evaluation, except quality of sleep, improved significantly more ($p<0.05$) for patients receiving estazolam or flurazepam than for those receiving placebo. The percentage of patients reporting any adverse experience was 59 percent for estazolam, 72 percent for flurazepam, and 43 percent for placebo. Somnolence and hypokinesia were the most commonly reported adverse

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events. An analysis of the global evaluation of side effects showed that flurazepam had a significantly worse side effect profile than estazolam ($p<0.05$) or placebo ($p=0.001$).

flurazepam and quazepam

Daytime residual drowsiness and psychomotor performance were assessed for quazepam and flurazepam in two randomized, parallel, double-blind studies in insomniacs.[137] In the first study, 17 middle-aged patients took quazepam 15 or 30 mg or flurazepam 30 mg nightly for four weeks. Subjects were given placebo for four nights before and 15 nights after active treatment. In the second study, 48 geriatric patients took quazepam 15 mg, flurazepam 15 mg, or placebo nightly for one week. Subjects were given placebo for one night before and seven nights after active treatment. In the first study, flurazepam patients were significantly ($p<0.05$) sleepier the day after the seventh and fourteenth treatment nights when compared to baseline, whereas quazepam patients were not. In the second study, flurazepam patients were sleepier in the late afternoon ($p<0.05$) after the seventh treatment night than were quazepam and placebo patients. There were no significant differences among the groups in the performance test results.

quazepam and triazolam

In a double-blind study, 45 patients were randomized to receive either quazepam 15 to 30 mg (median 15 mg) or triazolam 0.25 to 0.5 mg (median 0.25 mg) for four weeks.[138] The subjects, who had insomnia based on a mild to moderate generalized anxiety disorder, received placebo for one week before and two weeks after treatment with active drug. Anxiety improved significantly with both drugs and remained improved throughout the two-week post-drug placebo phase; quazepam was slightly superior to triazolam. Polysomnography, an objective measure of SOL, demonstrated a shortened sleep onset only after quazepam. Sleep efficiency improved after acute administration of both drugs, but improvement was maintained only by quazepam as tolerance developed to triazolam. Rebound insomnia was observed only in the first post-triazolam placebo night. Subjective sleep quality behaved very similarly to objective sleep efficiency. Awakening quality improved after acute therapy with both drugs. Somatic complaints were reported only with quazepam.

A randomized, double-blind, three-compartment, parallel-group study comparing quazepam 15 mg, triazolam 0.5 mg, and placebo was conducted in 65 insomniac subjects over five weeks.[139] Using sleep questionnaires for evaluation, no differences were noted between quazepam and triazolam on treatment nights. Evidence of carryover effectiveness with quazepam and rebound effects with triazolam was noted on off-treatment nights.

Comparisons of Benzodiazepines and Non-benzodiazepines

temazepam and zolpidem (Ambien)

A randomized, double-blind trial compared zolpidem 10 mg to temazepam 20 mg with respect to subjective rebound insomnia after cessation of four weeks of treatment of 163 patients with chronic insomnia.[140] Both agents improved total sleep time (TST) as well as SOL significantly during the four treatment weeks. Prevalence rates for rebound insomnia, defined as a worsening of TST or SOL of more than 40 percent compared to baseline, were 27 percent for TST and 53 percent for SOL in the zolpidem group and 26 and 58 percent, respectively, in the temazepam group. No significant differences were found between the agents for rebound insomnia, nor with respect to their efficacy or safety.

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triazolam and zaleplon (Sonata)

Zaleplon and triazolam were compared in a double-blind, placebo-controlled trial enrolling 132 patients with primary insomnia.[141] Patients received zaleplon 5 mg or 10 mg, triazolam 0.25 mg, or placebo for 14 nights. Median SOL was shorter in both zaleplon groups and triazolam group compared to placebo during the first week of therapy, but not during the second week due to a significant placebo effect. The effects of zaleplon on SOL were similar in the first and second weeks. Total sleep time did not differ between zaleplon and placebo groups. Total sleep time was increased during the first week of triazolam treatment, but not the second. On subjective assessment of SOL, zaleplon 10 mg and triazolam were more effective than placebo during the first week. Only zaleplon 10 mg produced lower subjective SOL during the second week. On the last night of assessment, none of the active treatments were judged more effective than placebo. Negative residual morning psychomotor or memory effects were not observed in any treatment group.

triazolam and zolpidem (Ambien)

In a parallel-group, double-blind, placebo-controlled, polysomnographic study, the possible occurrence of rebound insomnia was evaluated in 24 patients suffering from moderate to severe chronic insomnia. Patients were randomized to either triazolam 0.5 mg, zolpidem 10 mg, or placebo.[142] Treatment duration was 27 nights, followed by three placebo-controlled withdrawal nights. Both drugs showed significant efficacy compared to placebo during the active treatment period. A trend toward tolerance was noted in the triazolam group but not in the zolpidem group. The increase in total sleep time in the zolpidem group was accompanied by an increase in the number of sleep cycles. When active treatment was discontinued, clear rebound insomnia was present in the triazolam group while it was not possible to observe any rebound in the placebo and zolpidem groups. Subjective feelings of the patients assessed by means of visual analog scale correlated well with polysomnographic data.

Comparisons of Non-benzodiazepines

zaleplon (Sonata) and zolpidem (Ambien)

In a double-blind study, 615 patients were randomized to receive zaleplon 5 mg, zaleplon 10 mg, or zaleplon 20 mg, zolpidem 10 mg, or placebo.[143] The four-phase study consisted of a prestudy washout period (one to three weeks), a single-blind placebo run-in period (seven nights), a double-blind treatment period (28 nights), and a single-blind placebo run-out period (three nights). In the 574 patients who completed the study, zolpidem significantly reduced SOL during weeks one through three, as did zaleplon 5 mg. Zaleplon 20 mg and zolpidem 10 mg significantly increased sleep duration during all four weeks of the double-blind treatment. No significant differences were observed in number of awakenings between the placebo and active treatment groups during the double-blind treatment periods. Scores for sleep quality were significantly better than placebo during week one with zaleplon 10 and 20 mg and for all weeks with zolpidem 10 mg. On the first night after treatment discontinuation, significantly more patients who received zolpidem experienced longer SOL relative to baseline and reported withdrawal effects (depressed mood, pain in muscles, peculiar taste, loss of memory, olfactory sensitivity). The most common adverse event in all treatment groups was headache. There were no significant differences in the frequency of treatment-emergent adverse events among the active treatment groups and the placebo group.

A randomized, double-blind, placebo-controlled, three-period, crossover design was used to study 37 adults with insomnia who received treatment during an experimental awakening four hours after

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bedtime.[144] The study objective was to assess the efficacy of zaleplon 10 mg and zolpidem 10 mg administered during experimental middle-of-the-night awakenings in patients with sleep maintenance insomnia using objective polysomnographic measures and to assess daytime residual sedation four to seven hours after dosing using sleep latency testing. Latency to persistent sleep and total sleep time before and after awakening were recorded. Compared with placebo, latency to persistent sleep after both zaleplon and zolpidem was shorter and total sleep time after administration of the drugs was longer. Significant differences from placebo were not found with zaleplon in daytime sedation measures. At four, five, and seven hours after zolpidem, sleep onset, measured by sleep latency testing, was shorter than after placebo. Self report measures of concentration and alertness and Digit Symbol Substitution Test scores after zolpidem were also lower than placebo. Zaleplon 10 mg and zolpidem 10 mg effectively shorten sleep latency and lengthen sleep duration after dosing when administered during experimental nocturnal awakening. Residual sedation was not detected as little as four hours after zaleplon 10 mg but was detected with zolpidem 10 mg up to seven hours after treatment.

Placebo Controlled Trials of Non-benzodiazepines

doxepin (Silenor) and placebo

A randomized, double-blind, parallel-group, placebo-controlled study was conducted in healthy adults with transient insomnia.[145] Subjects received a single nighttime dose of placebo (n=282) or doxepin 6 mg (n=283) in a sleep laboratory. Efficacy was evaluated objectively by polysomnography and subjectively by morning questionnaire. The primary endpoint was latency to persistent sleep (LPS). Secondary polysomnography endpoints included wake after sleep onset (WASO), total sleep time (TST), wake time after sleep (WTAS), and sleep efficiency (SE). Doxepin demonstrated statistically significant improvements in LPS (13-minute decrease; $p<0.0001$), WASO (39 minutes less; $p<0.0001$), TST (51 minutes more; $p<0.0001$), WTAS ($p<0.0001$), overall SE ($p<0.0001$), and SE in each quarter of the night ($p<0.0001$), all versus placebo. There was no consistent evidence of residual sedation or minor sleep stage alterations. The incidence of doxepin adverse events was comparable to placebo.

A randomized, double-blind, parallel-group, five week placebo-controlled trial was conducted in adults diagnosed with primary insomnia and reported difficulty maintaining sleep (n=229).[146] Wake time after sleep onset (WASO) on the first night was identified as the primary outcome measure, and both active doses, (3 mg and 6 mg), resulted in statistically significant reductions in WASO ($p< 0.0001$). Subsequent WASO measurements were also statistically significant including on night 15 (3 mg $p=0.0025$; 6 mg $p=0.0009$), and night 29 (3 mg $p=0.00248$; 6 mg $p=0.0009$). Other secondary endpoints with significant improvement compared to placebo included latency to persistent sleep (3 mg $p=0.0047$; 6 mg $p=0.0007$) on night 1 only, and Total Sleep Time on nights 1 (both doses $p<0.0001$), and 29 (3 mg $p=0.0261$; 6 mg $p<0.0001$). Although most measures were statistically significant two measures did not reach significance for the 3 mg capsule. Both Sleep efficiency (SE) on the 29th night, and total sleep time on night 15 did not reach statistical significance. In contrast to benzodiazepine and other non-benzodiazepine hypnotics there was no evidence of rebound insomnia when doxepin was discontinued.

eszopiclone (Lunesta) and placebo

A double-blind study enrolled 308 patients, 21 to 64 years of age, with primary chronic insomnia.[147, 148] Patients were randomized to receive eszopiclone 2 mg, eszopiclone 3 mg, or placebo for 44 consecutive nights followed by two nights of single-blind placebo. Treatment with either dose of

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eszopiclone resulted in an approximate 45-minute improvement in the primary endpoint of SOL (placebo 58 minutes; p<0.001 for both doses). Eszopiclone also significantly improved the secondary endpoint of sleep efficiency (p<0.0001 for both doses compared to placebo). Another secondary endpoint, wake time after sleep onset (WASO), was reduced only by the higher dose of eszopiclone (41.2 minutes) compared to placebo (49.1 minutes; p=0.02). There was no evidence of tolerance or rebound insomnia after therapy discontinuation. There was no decrement in psychomotor performance relative to baseline, nor was there a difference between eszopiclone and placebo. The most common adverse event related to eszopiclone was unpleasant taste.

A double-blind study randomized 231 patients, 65 to 85 years of age, with chronic insomnia to receive either eszopiclone 1 mg, eszopiclone 2 mg, or placebo nightly for two weeks.[149, 150, 151] In the study, the higher dose of eszopiclone improved sleep maintenance (p<0.05), total sleep time (by 40 minutes; p<0.001), quality of sleep (p<0.001), depth of sleep (p<0.002), and reduced the number of naps (median 0 versus 2, p<0.05) compared to placebo. Patients receiving the higher dose also reported significant improvements in daytime alertness, daytime ability to function, sense of well being, and reduced morning sleepiness (p<0.05 for all comparisons to placebo). Both doses of eszopiclone were effective at decreasing SOL (p<0.004 compared to placebo) and reducing total nap time (p<0.05 compared to placebo).

In a double-blind study, 264 patients, 65 to 85 years of age, with a diagnosis of primary insomnia were randomized to receive eszopiclone 2 mg or placebo nightly for two weeks.[152] Compared with placebo, eszopiclone 2 mg significantly reduced objective (polysomnographic) and subjective SOL [(p<0.0001 for both measurements) and (p<0.05 and p=0.0019, respectively)]. Subjective improvement was also noted in sleep efficiency (p<0.04), total sleep time (p<0.0001), and the cumulative number and duration of naps among patients who napped (p=0.03) compared to placebo. Eszopiclone also produced improvements in the quality of sleep and in physical functioning. There was no rebound insomnia after treatment withdrawal, and the most common adverse event was unpleasant taste.

In a double-blind study, investigators randomized 545 patients with insomnia and major depressive disorder to receive, in addition to daily fluoxetine, eszopiclone 3 mg or placebo nightly.[153] In the eight-week study, patients treated with eszopiclone showed improvements in the primary endpoint, wake time after sleep onset ($p \leq 0.002$), compared to those receiving placebo. The active treatment was also more effective than placebo in improving the secondary endpoints of SOL ($p \leq 0.0001$) and TST ($p \leq 0.0004$). Patients in the eszopiclone group reported superior subjective improvements in sleep quality ($p \leq 0.0002$), depth of sleep ($p \leq 0.0007$), daytime alertness (p=0.03), clarity of thought and concentration (p=0.02), and ability to function (p=0.007). Patients in the eszopiclone group demonstrated significantly greater improvement in symptoms of depression, as measured by HAM-D17 (Hamilton Depression Rating Scale), at weeks four (p=0.01) and eight (p=0.002). HAM-D17 response were noted in 59 percent of patients in the eszopiclone group compared to 48 percent of patients in the placebo group; remission rates were 42 and 33 percent, respectively (p=0.03). Study completion rates and treatment tolerability were similar between groups.

A multicenter, randomized, double-blind, placebo-controlled trial evaluating eszopiclone treatment upon patient-reported sleep, fatigue and sleepiness, insomnia severity, quality of life, and work limitations for six months.[154] A total of 830 patients with primary insomnia, who reported mean nightly total sleep time $\leq$ 6.5 hours/night and/or mean nightly sleep latency >30 minutes were randomized to eszopiclone 3 mg or matching placebo for six months. Patient-reported sleep and daytime function,

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Insomnia Severity Index, Physical Functioning, Vitality, and Social Functioning, and Work Limitations Questionnaire domain scores were improved with eszopiclone versus placebo (all p<0.05).

ramelteon (Rozerem) and placebo

In a double-blind study, investigators randomized 829 elderly patients (mean age 72.4 years) with chronic primary insomnia to either ramelteon 4 mg, ramelteon 8 mg, or placebo nightly for five weeks.[155] Administration of ramelteon resulted in a reduction in subjective SOL and an increase in TST at weeks one, three, and five of the study. Ramelteon did not change subjective sleep quality, the number of nighttime awakenings, or the ease of falling back to sleep. Withdrawal effects, including rebound insomnia, were not observed.

In a double-blind study, 405 patients (mean age 39.3 years) with primary insomnia were randomized to receive ramelteon 8 mg, ramelteon 16 mg, or placebo nightly for 35 nights.[156] Polysomnography indicated that both doses of ramelteon were associated with a reduction in SOL at each assessment starting on nights one and two. Ramelteon was also associated with an improvement in TST and sleep efficiency on nights one and two.

A six-month, randomized, double-blind, placebo-controlled, multicenter study evaluated the long-term efficacy of ramelteon for insomnia in 451 adults (age ≥ 18 years) with chronic primary insomnia.[157] Patients were randomized to receive either ramelteon 8 mg or placebo 30 minutes before bedtime nightly for six months. Sleep was evaluated by polysomnography and morning questionnaires on the first two nights of week one; the last two nights of months one, three, five, and six; and nights one and two of the placebo run-out. Next-morning residual effects as well as adverse effects and vital signs were recorded at each visit. Rebound insomnia and withdrawal effects were evaluated during placebo run-out. During the six months of treatment, ramelteon consistently reduced latency to persistent sleep compared with baseline and with placebo; significant decreases were observed at week one and months one, three, five, and six (p<0.05). Ramelteon significantly reduced subjective sleep latency relative to placebo at week one, month one, and month five (p<0.05), with reductions nearing statistical significance at months three and six (p≤0.08). No significant next-morning residual effects were detected during ramelteon treatment. No withdrawal symptoms or rebound insomnia were detected after ramelteon discontinuation. Most adverse events were mild or moderate in severity.

tasimelteon (Hetlioz) and placebo

The effectiveness of tasimelteon was evaluated in 104 patients in two randomized, double-masked, placebo-controlled, clinical trials of totally blind individuals with non-24 disorder.[158] Patients were randomized to receive tasimelteon or placebo one hour prior to bedtime, at the same time every night.

In Study 1 (Safety and Efficacy of Tasimelteon [SET]), 84 patients with non-24 were randomized to receive tasimelteon 20 mg or placebo, one hour prior to bedtime, at the same time every night for up to six months. Study 2 (Randomized Withdrawal Study of the Efficacy and Safety of Tasimelteon [RESET]) was a randomized withdrawal trial in 20 patients with non-24 to evaluate the maintenance of efficacy. Patients were treated initially for approximately 12 weeks. Patients in whom the calculated time of peak melatonin level occurred at approximately the same time of day (in contrast to the expected daily delay) during the run-in phase were randomized to receive placebo or continue treatment for eight weeks.

Study 1 and Study 2 evaluated the duration and timing of nighttime sleep and daytime naps via patient-recorded diaries. Because symptoms of nighttime sleep disruption and daytime sleepiness are

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cyclical in patients with non-24, with severity varying, efficacy endpoints for nighttime total sleep time and daytime nap duration were based on the 25 percent of nights with the least nighttime sleep, and the 25 percent of days with the most daytime nap time. In Study 1, patients had, at baseline, an average 195 minutes of nighttime sleep and 137 minutes of daytime nap time on the 25 percent of most symptomatic nights and days, respectively. Treatment with tasimelteon resulted in a significant improvement, compared with placebo. In Study 1, mean total nighttime sleep was 28 minutes longer and daytime nap time was 27 minutes shorter in the tasimelteon group compared to placebo. In Study 2, synchronization was maintained in 90 percent of the tasimelteon group versus 20 percent of placebo. Mean total nighttime sleep was 67 minutes longer and daytime nap time was 59 minutes shorter in the tasimelteon group compared to placebo,

A responder analysis of patients with both ≥ 45 minutes increase in nighttime sleep and ≥ 45 minutes decrease in daytime nap time was conducted in Study 1: 29 percent (n=12) of patients treated with tasimelteon, compared with 12 percent (n=five) of patients treated with placebo met the responder criteria.

zolpidem (Intermezzo) and placebo

A randomized, double-blind, placebo-controlled, three-way crossover study evaluated the efficacy and safety of low-dose, sublingual zolpidem tartrate when taken during a scheduled middle-of-the-night (MOTN) awakening in subjects with insomnia characterized by difficulty returning to sleep following MOTN awakenings.[159] The study was performed at five sleep laboratories and enrolled adults (24 males, 58 females, mean age 45.9 years) with a diagnosis of DSM-IV primary insomnia and a history of prolonged MOTN awakenings. Baseline difficulties with MOTN awakenings were confirmed by a ten-day screening sleep diary and polysomnography (PSG) screening. Each treatment period consisted of two consecutive nights of dosing separated by a washout period of five to 12 days. Subjects were awakened four hours after lights out, dosed with sublingual zolpidem 3.5 mg, zolpidem 1.75 mg, or placebo, kept awake for 30 minutes, and then returned to bed for an additional four hours. Sleep parameters were assessed by PSG and post-sleep questionnaires. Results demonstrated that low-dose sublingual zolpidem tartrate demonstrated significant dose-related decreases in latency to persistent sleep and total sleep time ($p<0.001$) compared to placebo after MOTN dosing. All subject reports paralleled PSG observations. Neither dose showed next-morning impairment on the digit symbol substitution test (DSST) or ratings of sleepiness. The 3.5-mg dose produced improvements in reports of sleep quality ($p<0.001$), ability to function, and level of refreshed sleep ($p<0.05$ for both dosages) compared to placebo. Sublingual zolpidem tartrate lozenges were generally safe and well tolerated.

In a randomized, double-blind, placebo-controlled outpatient as-need study, adults aged 18 to 64 years (n=295; 201-female; 94 male) with a history of problems returning to sleep after MOTN awakenings were evaluated in a four week study using zolpidem tartrate.[160] Patients used either 3.5 mg zolpidem tartrate or placebo (as needed) following episodes of MOTN waking with difficulties in returning to sleep. Patients were required to have at least four hours of time to remain in bed following zolpidem dosing. The results were patient evaluations of the time to return to sleep following as needed dosing were significantly shorter for zolpidem 3.5 mg than placebo.

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zolpidem (Zolpimist) and placebo

In a double-blind, parallel-group, single-night trial in adults experiencing transient insomnia (n=462), zolpidem 7.5 mg or 10 mg or placebo were compared.[161] Both zolpidem doses were superior to placebo by measure of sleep latency, sleep duration, and number of awakenings.

zolpidem ER (Ambien CR) and placebo

Two similar three-week studies of zolpidem ER were conducted in patients with primary insomnia.[162, 163] One study randomized 205 elderly patients (mean age 70.2 years) to zolpidem ER 6.25 mg or placebo while the other randomized 212 adults (mean age 44.3 years) to zolpidem ER 12.5 mg or placebo. In each study, zolpidem ER was found to lead to significant improvement compared to placebo in polysomnographic WASO in the first six hours of the night as well as improvement in SOL and TST. Subjects did not report any residual impairment or sedation.

SUMMARY

The selection of a specific hypnotic is based in large part on whether the patient has problems with initiation or maintenance of sleep, co-morbid conditions, side effect tolerance, and availability. Sedative hypnotics should be prescribed at the lowest dose that treats the patients' symptoms.

The assumed increased risk with benzodiazepine medications over non-benzodiazepines is based on indirect comparisons, and there is evidence of publication bias as both groups have increased incidence of adverse risks in patients over 60 years of age.

In general, the benzodiazepines decrease the time for sleep onset and prolong the duration of sleep, although dependence, tolerance, and abuse may occur. Among the benzodiazepines, the duration of action is the primary variable that may make one preferable to another in a given patient. Triazolam has the shortest duration of action, while temazepam and estazolam have intermediate durations. Flurazepam and quazepam have long durations of effect, and as a result, should be avoided in the elderly or others in whom daytime sedation may be a concern.

Rebound insomnia may develop when benzodiazepines are abruptly withdrawn and is more likely to occur with the short-acting benzodiazepines. Rebound insomnia can be minimized by using smaller doses and tapering the dosage. Some studies have highlighted concerns with increased falls and hip fractures in the elderly following benzodiazepine use; however, others have found that untreated insomnia itself increases the risk of falls.

Similar to the benzodiazepines, the BZ-1 selective agents decrease sleep latency with duration of action again being the primary difference among these agents. Although dependence, tolerance and abuse may occur with these agents, next day sedation, rebound insomnia, and drug interactions are generally lessened. For the BZ-1 selective agents, zaleplon is more rapid acting with a shorter duration than zolpidem. Eszopiclone has a longer half-life than either zaleplon or zolpidem. Specialized formulations of zolpidem (Edluar, Zolpimist, Intermezzo) do not have a significant clinical advantage over tablets. Additionally, due to gender differences in zolpidem clearance, women require lower doses of zolpidem.

Doxepin (Silenor) appears to have some success in treating insomnia, particularly in cases where sleep latency and not sleep initiation is the issue. Patients experiencing problems with sleep latency who

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have not achieved success with more common sedative/hypnotic agents may benefit from doxepin. However, in general no data are present to suggest doxepin is superior to other agents in this class.

The melatonin receptor agonist, ramelteon (Rozerem), has demonstrated reduction in sleep latency, but not in sleep maintenance. Patient evaluations are inconsistent, and there are no direct comparative studies. There is a low likelihood of dependence or abuse, and adverse effects are rare.

Tasimelteon (Hetlioz) a melatonin receptor agonist pharmacologically similar to ramelteon (Rozerem), is approved for non-24 in totally blind patients. Due to differences in circadian rhythms, it can take weeks or months of daily use of tasimelteon before the patient experiences any benefit. Comparisons to ramelteon or melatonin are lacking.

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